CERTARA

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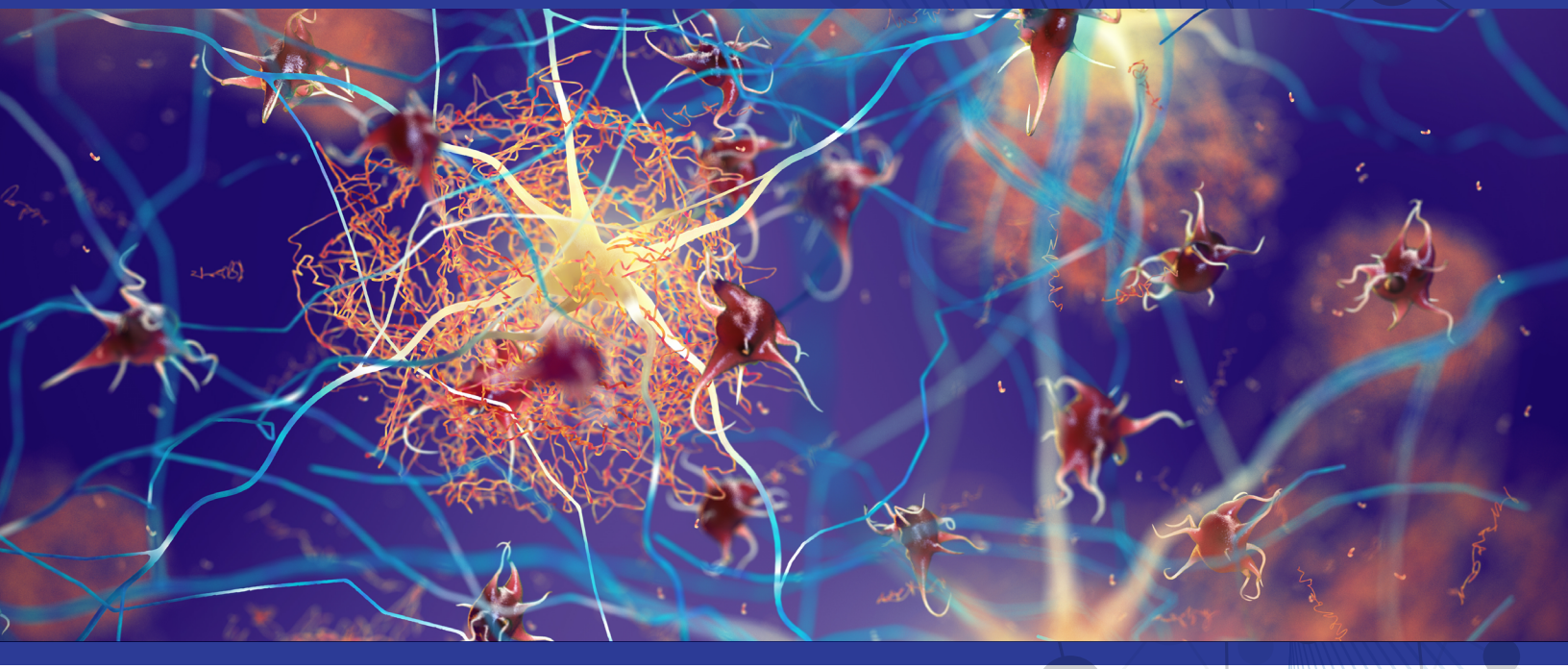

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THIS WORK REPRESENTS THE FIRST *IN-SILICO* APPROACH IN SUPPORT OF A SUCCESSFUL AD THERAPY

The accelerated approval of lecanemab in January 2023 confirmed that amyloid modulating agents are today's most advanced disease-modifying approaches for Alzheimer's Disease (AD). FDA's approval was based on the changes in SUVr amyloid load biomarker, which has been recognized by the agency as a surrogate marker for efficacy. Global brain amyloid load can be measured using the PET amyloid imaging biomarkers, but other more accessible plasma biomarkers are also of practical importance.

Working with the sponsor, Certara built a Physiologically-based Pharmacokinetics/Quantitative Systems Pharmacology (PBPK/QSP) model to predict safety and biomarker outcomes via a mechanistic-based platform for lecanemab. Based on the unique PK properties and pharmacology of this new drug, Certara's model correctly predicted efficacy biomarker outcomes and generated a new hypothesis for the relatively lower Amyloid-Related Imaging Abnormalities (ARIA-E) liability of lecanemab. To maximize amyloid SUVr reduction and minimize ARIA-E side-effect liability for any new drug profile.

In addition, we were able to predict changes in brain amyloid load (pharmacodynamics) by modeling, identifying a less expensive and invasive approach to positron emission tomography (PET) scans. This model has demonstrated its predictive ability and can play an important role in the R&D and regulatory approaches for new AD drugs.

The Certara model answered several pivotal questions:

- What is the impact of the pharmacology and antibody isotype on the SUVr biomarker outcome?
- What is the optimal dose and titration strategy for maximizing SUVr change and minimizing ARIA-E liability?
- How do changes in plasma and CSF fluid biomarkers relate to changes in SUVr?
- How does APOE4 genotype, age and gender affect both the biomarker outcomes and the ARIA-E liability?
- Can we differentiate antibody performance?
- What is driving ARIA-E liability?
- Can we begin to identify responder populations for amyloid modulators?

APPROACH

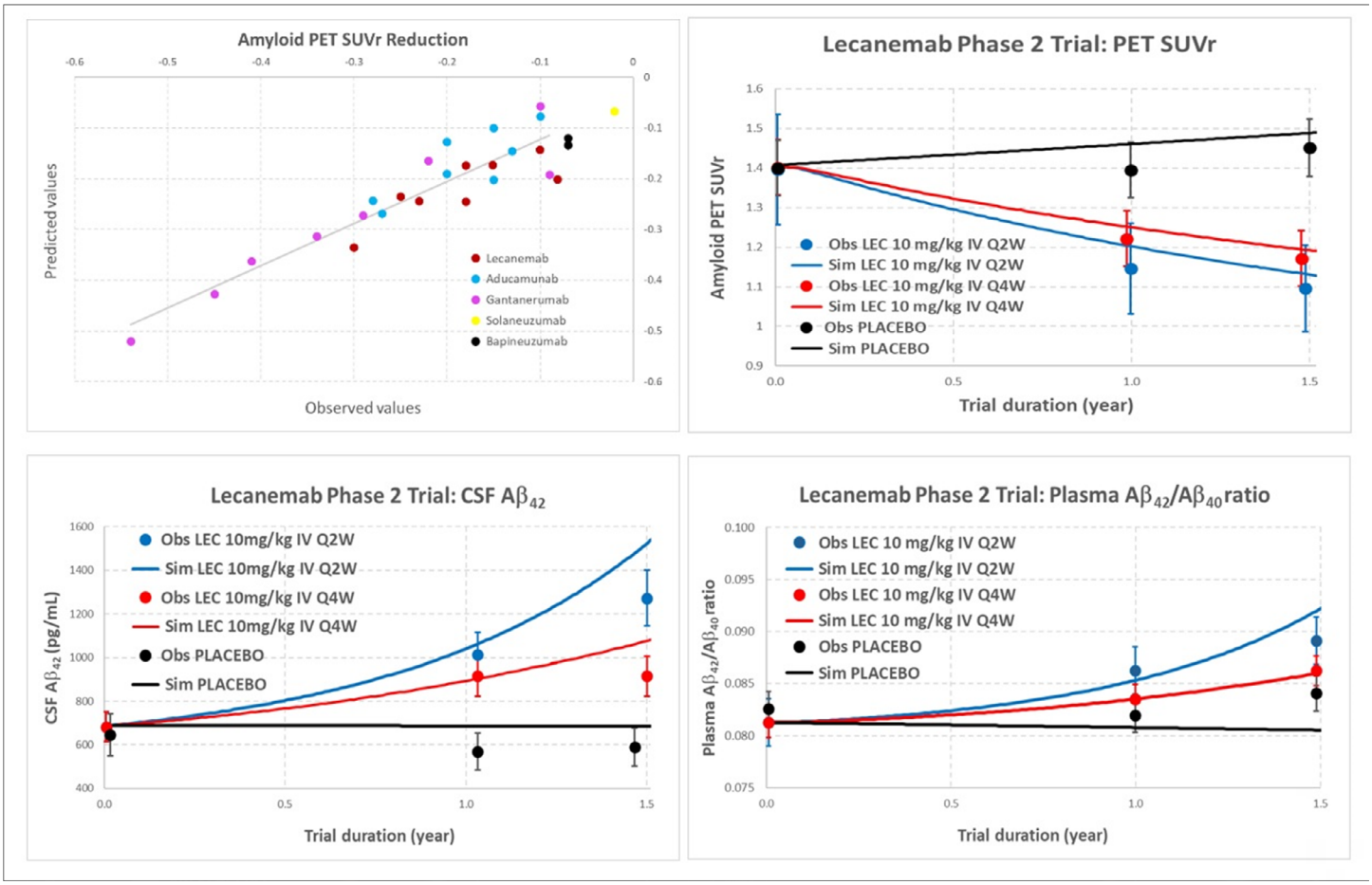
Certara's approach integrated the dynamics of Aβ monomers, oligomers, protofibrils and plaque using a detailed microscopic model of Aβ40 and Aβ42 aggregation and clearance of aggregated Aβ by activated microglia cells, which is enhanced by the interaction of antibody-bound Aβ. The model allows for the prediction of Aβ PET imaging load as measured by Standardized Uptake Value Ratio (SUVr). A PBPK model is seamlessly integrated to describe target exposure of monoclonal antibodies and simulate dynamics of cerebrospinal fluid (CSF) and plasma biomarkers, including CSF Aβ42 and the ratio of plasma Aβ42/Aβ40 biomarkers. APOE genotype is implemented as a difference in microglia clearance. By incorporating antibody-bound plaque mediated macrophage activation in the perivascular compartment, the model also simulates the incidence of ARIA-E.

Longitudinal changes in an AD patient were simulated using an age-dependent decrease in Aβ monomer clearance and qualitatively recapitulate the time-dependent relationship between fluid biomarkers of plasma and CSF Aβ42 and brain amyloid load. Besides quantitatively capturing the delay in biomarker changes between APOE4 and non-APOE4 genotype subjects, the model also predicted absolute values of the measured biomarkers.

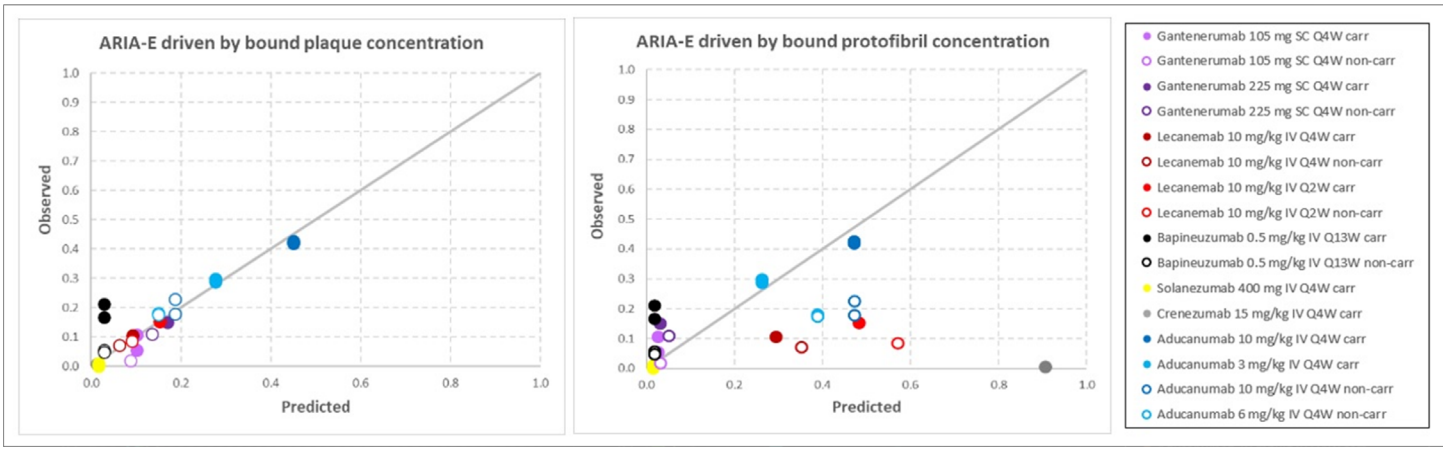
The QSP platform was calibrated with pharmacological and clinical information on six unique compounds, including lecanemab.

RESULTS OF THE QSP SIMULATIONS

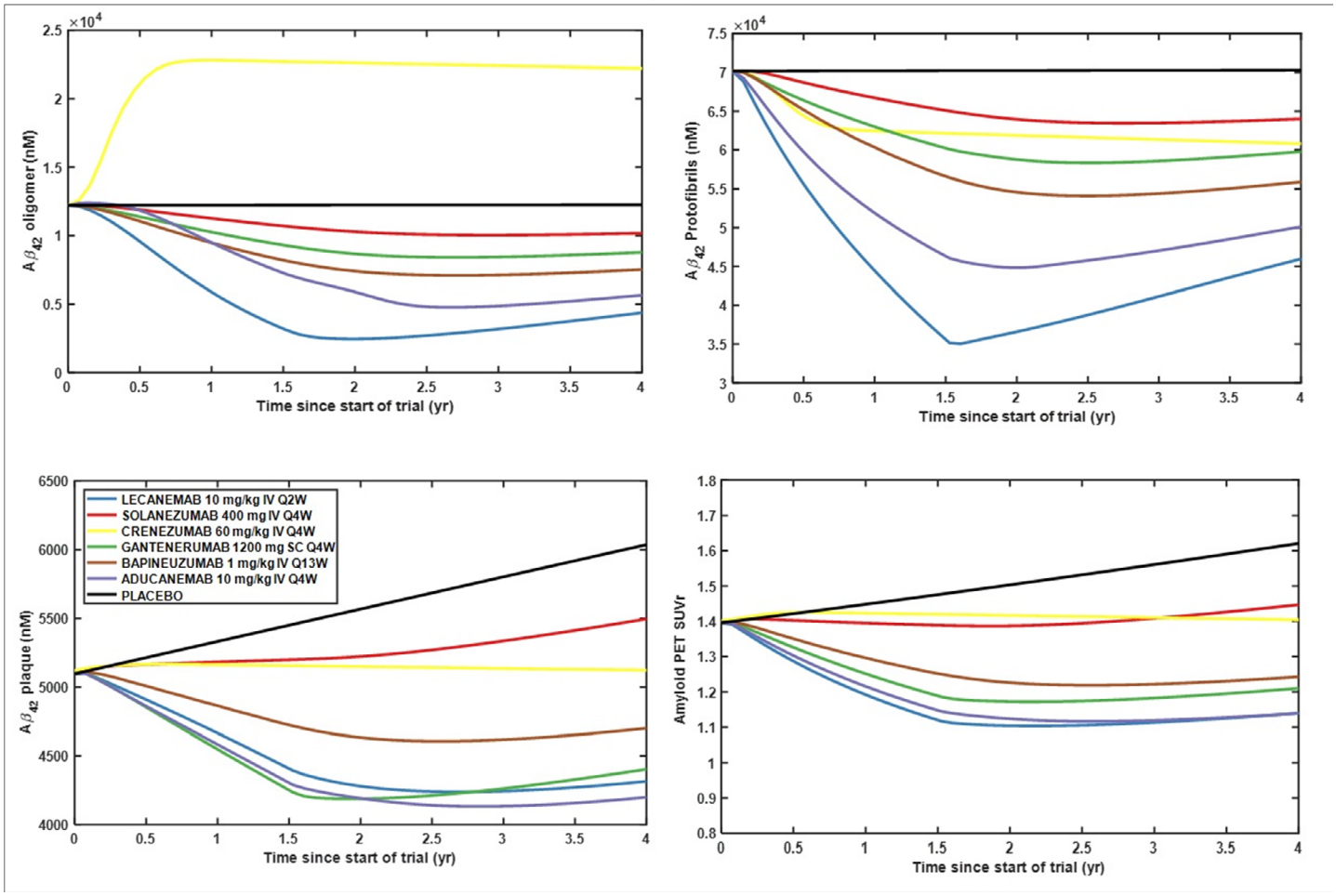
- Using the affinities for different Aβ forms, we simulated the clinical trial data for 25 different readouts of amyloid antibody interventions at different doses and time-points. The figure (top left) below shows a robust correlation between predicted and observed changes in SUVr, while the top right graph adequately describes the time-dependent observed changes for aducanumab's Phase 3 trials. The bottom graphs illustrate the capability of predicting changes in CSF Ab42 and plasma Ab42/Ab40 ratio after lecanemab treatment.



- We used our model to simulate ARIA-E events based on the clinical trial designs for six different antibodies and compared the results to the reported values at the end of the respective trial duration. Moreover, by implementing a time-to-event approach, the model was able to capture the time dependent increase of ARIA-E liability which was more pronounced in the first weeks of treatment, as observed in the clinical trials. The figure suggests that the observed ARIA-E liability correlated much better with the amount of antibody bound to plaques in the perivascular compartment than the amount of antibody bound to protofibrils. This generates an interesting hypothesis that could be useful in the optimization of the pharmacology for new anti-amyloid antibodies.



- An interesting readout of the model are the 'experimentally inaccessible' profiles of oligomers and protofibrils from the observed SUVR dynamics, as there is increasing evidence that the insoluble forms, rather than the plaques, might drive the neuropathology in AD. These profiles naturally flow out from the mechanism-based derivation of the aggregation kinetics. The figure below shows the dynamics of oligomers, protofibrils and plaques associated with a specific decrease in SUVr for several therapeutic interventions. It clearly suggests that the same SUVr reduction can be achieved by different combinations of oligomer, protofibril and plaques dynamics, providing a possible explanation for the differential cognitive effects of the various antibodies.



APPLICATIONS OF THE MODEL

- Prediction of the optimal titration schedule that would minimize the incidence of ARIA-E at the same time as increasing the likelihood of changes in amyloid biomarkers.
- Trajectory of biomarkers after treatment halt, either at a specific pre-defined time or after detection of an ARIA-E side-effect.
- The impact of baseline amyloid load, age, and gender on the pharmacodynamics of SUVR, ARIA-E and fluid biomarkers.
- Mitigating compliance issues
- Identification of optimal maintenance dose after treatment.
- Simulation of the pharmacodynamic effect of amyloid antibodies as standard of care (SoC) in future combination trials.

SUMMARY

To support the development of lecanemab, we developed a QSP model based on the biology of Aβ40 and Aβ42 synthesis and degradation, their aggregation into higher order oligomers, protofibrils and plaques, clearance by microglia cells, and the impact of the APOE4 genotype.

- The model enabled us to identify differences in antibody response both at the level of biomarker changes as well as ARIA-E liability.
- The model suggests that the relative affinity of the antibody for the protofibrils and plaques is a major determinant for the liability of ARIA-E during treatment.
- A well validated readout for predicted change in brain function (pharmacodynamics) is the Abeta42/Abeta40 ratio plasma biomarker, identifying a less expensive and invasive approach to PET scans.
- This QSP model could support clinical trial design of different amyloid modulating interventions, define optimal titration and maintenance schedules, support future combination trials, address treatment interruption due to ARIA-E or compliance issues and provide a first step to understand the variability of biomarker response in clinical practice.

Full published paper can be accessed at: https://ascpt.onlinelibrary.wiley.com/doi/abs/10.1002/psp4.12912

About Certara

Certara accelerates medicines using proprietary biosimulation software, technology and services to transform traditional drug discovery and development. Its clients include more than 2,000 biopharmaceutical companies, academic institutions and regulatory agencies across 62 countries.

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